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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/995,519	11/28/2001	Vassiliki A. Boussiotis	RPI-011CPCN	3634

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EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 06/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/995,519	BOUSSIOTIS ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 11/28/01

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☑ Claim(s) 92-107 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☑ Claim(s) _____ is/are rejected. 92-107

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☑ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5)☐ Notice of Informal Patent Application (PTO-152)

6)☐ Other: _____.

DETAILED ACTION

1. Applicant's amendments, filed 11/28/01, have been entered.
Claims 1-91 have been canceled.
Claims 92-107 have been added.

Given the prosecution and issued claims from the parent application USSN 08/457,783, now U.S. Patent No. 6,451,305, claims 92-107 are being acted upon.

2. If applicant desires priority under 35 U.S.C. 120 based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No._____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

Applicant should amend the first line of the specification to update the status (and relationship) of the priority documents.

Also see United States Patent and Trademark Office OG Notices: 1268 OG 89 (18 March 2003).

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant should restrict the title to the claimed invention.

4. The Abstract of the Disclosure is objected to because it does not adequately describe the claimed invention. Correction is required. See MPEP 608.01(b).

5. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

Trademarks should be capitalized or accompanied by the ™ or ® symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate corrections are required

6. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 92-107 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.
This is a written description rejection.

The specification broadly describes and the claims recite as part of the invention the following:
A "CD2 ligand" and a "CD28 ligand or CTLA-4 ligand".

Although the specification discloses LFA-3/CD58 (the elected species) as well as CD48 and CD59 as CD2 ligands (see Section III. Methods of Restoring T cell responsiveness, starting on the bottom of page 15 of the specification; e.g. page 16, paragraph 3); there is insufficient structural information that defines other CD2 ligands that modify tumor cells to stimulate T cells.

Although the specification discloses B7-1 or B7-2 as the CD28-/CTLA-4-ligand (Section IV Methods for Restoring a T cell response to Antigen, stating on page 22 of the specification; e.g. page 22, paragraph 3); there is insufficient structural information that defines other CD28-/CTLA-4-ligands that modify tumor cells to stimulate T cells.

In addition, the specification broadly describes and the claims recite as part of the invention the following: "agent that stimulates exposure of a T11.3 neo-epitope on a CD2 surface receptor on the T cell.

Although the specification discloses that anti-CD2 antibodies or IL-2/IL-4 can stimulate the T11.3 epitope (see pages 20-21, Priming of an Unresponsive T cells); there is insufficient structural information that defines other agents that stimulates exposure of a T11.3 neo-epitope on a CD2 surface receptor on the T cell in order to stimulate T cells in response to modified tumor cells.

The specification as filed does not provide written description support for the structural characteristics that define the claimed CD2 ligand and a CD28 ligand or CTLA-4 ligand as well as the claimed "agents" that stimulate exposure of a T11.3 neo-epitope on a CD2 surface receptor on the T cell; other than those disclosed in the specification as filed.

The skilled artisan cannot envision the contemplated the detailed chemical structure of the claimed protein and therefore conception cannot be not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF=s were found unpatentable due to lack of written description for the broad class.

In Fiers v. Sugano; it was stated: "An adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself" (26 USPQ2d 1601 at 1606). Thus, the instant specification does not adequately describe, and therefore *cannot* adequately teach how to make, the claimed invention.

"It is not sufficient to define the recombinant molecule by its principal biological activity, e.g. having protein A activity, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property." Colbert v. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992).

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.) Applicants are directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, & 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999.

The disclosed CD2 ligands LFA-3/CD58, CD49 and CD59 as well as the CD28-/CTLA-4-ligands B7-1 and B7-2 meet the written description provision of 35 USC 112, first paragraph.

In addition, the disclosed IL-2/IL-4 cytokines as well as anti-CD2 antibodies meet the written description provision of 35 USC 112, first paragraph, for "agents".

However, the instant claims do not provide functional characteristics coupled with a known or disclosed correlation between function and structure. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variable, the recitation of "CD2 ligand", "CD28 ligand", "CTLA-4 ligand" and "agents" alone is insufficient to provide sufficient written description of the claimed genuses.

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species; then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3rd column).

In the absence of functional characteristics that are shared by members of the genuses of "CD2 ligand", "CD28 ligand", "CTLA-4 ligand" and "agents", one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genuses. See University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997).

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

8. Claims 92-107 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "LFA-3/CD58, CD49 and CD59" as CD2 ligands and B7-1 and B7-2" as the CD28-/CTLA-4-ligands does not reasonably provide enablement for any CD2 ligand or CD28-/CTLA-4-ligands.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims.

Applicant has not provided sufficient biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies ligands other than those encompassed by "LFA-3/CD58, CD49 and CD59" as ACD2 ligands and "B7-1" and "B7-2" as the ACD28-/CTLA-4-ligands@.

An alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property (e.g. structural or functional). Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use of the claimed ligands in manner reasonably correlated with the scope of the claims to stimulate T cells response to transfected tumor cells.

Further, since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and still retain similar activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. Minor structural differences among structurally related compounds or compositions can result in substantially different pharmacological activities. Therefore, structurally unrelated compounds encompassed by the claimed CD2/CD28/CTLA-4 ligands would be expected to have greater differences in their activities.

Here applicant has not provided the defining structural or correlative teachings sufficient to enable one of skill to isolate and identify the ligands with the appropriate structural characteristic or property of the instant ligands to the extent that one of skill would be able to predictably identify the claimed ligands. It is noted that the known CD2/CD28/CTLA-4 ligands differ with respect to structure to the extent that the skilled artisan would not envision one in view of the other. Even those these ligands have overlapping functional properties, these ligands differ with respect to structure and function.

Since the disclosure fails to describe the common structural attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of a limited number of ligands and the ability to screen, is insufficient to enable the genus, encompassed by the claimed invention.

The problem of predicting protein structure from such limited information of a limited number of known ligands protein and, in turn, utilizing predicted structural determinations to ascertain functional aspects of other ligands, including unknown ligands and finally what changes can be tolerated with respect thereto is extremely complex and well outside the realm of routine experimentation.

Insufficient direction or guidance is provided to assist one skilled in the art in the selection of any CD2 or CD28/CTLA-4 ligands other than those disclosed in the specification as filed nor is there evidence provided that other such ligands can bind CD2 or CD28/CTLA-4 and stimulate T cell responses to tumor cells. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, making and using CD2 or CD28CTLA-4 ligands would be unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

9. Claims 98 and 101-107 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "anti-CD2 antibodies and IL-2/IL-4 as agents that stimulate exposure of a T11.3 neo-epitope on a CD2 surface receptor on the T cell"; does not reasonably provide enablement for any "agents that stimulate exposure of a T11.3 neo-epitope on a CD2 surface receptor on the T cell".

The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims.

Applicant has not provided sufficient biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies "agents that stimulate exposure of a T11.3 neo-epitope on a CD2 surface receptor on the T cell" other than those encompassed by "anti-CD2 antibodies or IL-2/IL-4".

For the reasons set forth above; applicant has not provided the sufficient defining structural or correlative teachings sufficient to enable one of skill to isolate and identify the "agents" with the appropriate structural characteristic or property of the instant "agents" to the extent that one of skill would be able to predictably identify the claimed "agents". It is noted that the known "agents" (e.g. anti-CD2 antibodies, IL-2 and IL-4) differ with respect to structure to the extent that the skilled artisan would not envision one in view of the other. Even those these ligands have overlapping functional properties, these ligands differ with respect to structure and function.

Insufficient direction or guidance is provided to assist one skilled in the art in the selection of any "agent that stimulate exposure of a T11.3 neo-epitope on a CD2 surface receptor on the T cell" other than those disclosed in the specification as filed nor is there evidence provided that other such "agents" that can stimulate exposure of a T11.3 epitope on a T cell response in order to stimulate T cell responses to tumor cells. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, making and using an "agent that stimulate exposure of a T11.3 neo-epitope on a CD2 surface receptor on the T cell" would be unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

10. A non-statutory double patenting rejection, whether of the obvious-type or non-obvious-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel,* 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam,* 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi,* 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman,* 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78 (d).

Effective January 1, 1994, a registered attorney or agent of record may sign a Terminal Disclaimer. A Terminal Disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 92-107 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 6,451,305 . Although the conflicting claims are not identical, the are not patentably distinct from each other because they are drawn to the same or nearly the same methods of stimulating T cell responses to tumor cells modified with the same or nearly the same CD2 ligands, CD28 ligands or CTLA-4 ligands. The patented claims anticipate the instant claims.

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phillip Gambel, PhD.
Primary Examiner
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June 28, 2004